REMARKS

I. Status of Claims and Formal Matters

Claims 1, 3-5, 7-12, 14-15, and 18-23 are pending in the application and stand rejected. No claim amendments, additions and/or cancellations are presented herein. Accordingly, claims 1, 7-9, 14, 15, 19-22 and 27-29 will remain pending in the application.

Reconsideration and withdrawal of the objections to and the rejections of this application in view of the remarks herewith, are respectfully requested.

Applicants respectfully reserve the right to pursue any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

II. The Rejections Under 35 U.S.C. § 103

A. Claims 1, 9, 14, 15, 19-22, and 27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over United States Patent No. 5,589,480 to Elkhoury, *et al.* ("Elkhoury"), in view of United States Patent No. 5,849,761 to Yaksh ("Yaksh"), United States Patent No. 5,840,731 to Mayer, *et al.* ("Mayer"), United States Patent No. 5,635,204 to Gervitz, *et al.* ("Gervitz") and T. Lin, *et al. Can. J. Anesth.* Feb. 1998, 45(2), pages 175-177 ("Lin"). Applicants respectfully disagree and traverse.

To properly determine a *prima facie* case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is important, as "impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." Id. Three basic criteria must then be met: first, there must be some suggestion or motivation to modify or combine the cited references; second, there must be a reasonable expectation of success; and third, the prior art references must teach or suggest all the claim limitations. M.P.E.P §2143. With regard to the first criterion, the "mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." M.P.E.P §2143.01 (citing *In re Mills*, 916 F.3d 690 (Fed. Cir. 1990)). "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render the claim obvious." *Graham v. John Deere Co.*,

383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002)]. The issue is whether substantial evidence supports the judgment (under the clear and convincing evidence standard) that a person having ordinary skill in the art would not have been motivated to replace the [prior art] combination ... with [the claimed combination.]" *Abbott Laboratories v. Syntron Bioresearch, Inc.*, 334 F.3d 1343, (Fed. Cir. 2003).

The claimed invention provides topical pharmaceutical compositions and methods of providing analgesia comprising morphine and a tolerance-attenuating dosage of ketamine sufficient to yield a dose-lowering effect on morphine.

The Examiner alleges that Elkhoury teaches a topical composition of morphine that provides an analgesic effect in a localized area without migration to the bloodstream. Elkhoury does not teach a combination of morphine and ketamine, let alone a tolerance-attenuating dosage of ketamine sufficient to yield a dose-lowering effect on morphine. Indeed, there is no discussion in Elkhoury of the effect of combining morphine with ***any*** other compounds. As such, one of ordinary skill in the art would have lacked an expectation of success that the morphine composition of Elkhoury could be combined with other active ingredients while still maintaining the localized effect without migration of the drug into the bloodstream described.

The Examiner relies on Yaksh, Mayer, Gervitz and Lin to rectify the deficiencies of Elkhoury. In particular, the Examiner alleges that: Yaksh teaches the use of low dosages of morphine to avoid CNS side effects; Mayer teaches the addition of ketamine to enhance analgesia and/or reduce side effects; Gervitz teaches the use of ketamine for topical administration; and Lin teaches the combination of ketamine, morphine and bupivacaine.

To that end, the Examiner's assertion appears to utilize impermissible hind-sight, using the present specification as a blueprint to reconstruct the claimed invention from the isolated teachings of the prior art. Indeed, the Examiner has chosen discrete disclosures from each of the **four** supplementary references – in some instances a single sentence taken out of context – to arrive at his conclusion without demonstrating where in each reference the motivation to combine the reference with the primary reference, let alone with the other supplementary references, is taught. Applicants respectfully remind the Examiner that hind-sight analysis is improper. See, e.g., *Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988).

With regard to Yaksh, the Examiner admits that Yaksh teaches the disadvantage of the use of morphine in that it is taught to have short duration of activity and to have systemic and CNS side effects when used at high levels. (See, Office Action – Paragraph 9). Applicants respectfully submit that Yaksh teaches away from the use of morphine at all. Indeed, Yaksh states that "other opioids, such as morphine, that readily cross the blood brain barrier could be effective as anti-hyperalgesiscs, but their permeability through the blood brain barrier results in abuse liability" (Column 4, lines 45-49) and that "the compositions provided herein, contain opioids that ***do not,*** upon topical or local administration, substantially ***cross the blood brain barrier...***" (Column, 4, lines 50-53). Indeed, morphine is not otherwise encompassed by the disclosure of Yaksh and is only used as a standard in the assays described. In view of this clearing teaching away, one of ordinary skill in the art would have lacked the motivation to combine Yaksh with Elkhoury to arrive at the claimed invention.

With regard to Mayer, the Examiner alleges that Mayer teaches that the analgesic effectiveness of a combination drug composition comprising at least one analgesic (for example, morphine)is significantly enhanced by the addition of an NMDA receptor antagonist (for example, ketamine). It is important to note that Mayer is limited to the discussion of compositions comprising both an analgesic (either opioid or non-opioid) and a second component chosen from a sedative, a muscle relaxant or a non-opioid analgesic. Mayer is silent as to the effect of an NMDA receptor antagonist on compositions of morphine alone. Nevertheless, although Mayer describes the ability of the NMDA receptor antagonist to "permit either a reduction in the amount of analgesic in a dosage unit without a reduction in the level of pain relief" (Column 2, lines 60-64), Mayer is silent as to the use of a tolerance-attenuating dosage of said NMDA receptor antagonist. Indeed, Mayer goes on to state that the NMDA inhibitor may also act to "increase ...the level of pain relief without an increase in the amount of analgesic in a dosage unit." (Column 2, lines 64-66). At best, the proposed combination is "obvious to try." However, it has long been established that "obvious to try" is not the standard of obviousness under 35 U.S.C. § 103. *In re Geiger*, 815 F.2d 686, 655 (Fed. Cir. 1987). Accordingly, one of ordinary skill in the art would not appreciate, based on a reading of Mayer, that morphine could be administered concurrently with a tolerance-attenuating dose of a ketamine to attenuate, reverse, or prevent tolerance to analgesics.

With regard to Gervitz, the Examiner alleges that Gervitz teaches the use of ketamine for topical administration. Applicants contend that Gervitz is directed to a method of inducing surgical anesthesia via transdermal administration of an amnesia-producing drug and, subsequently, an anesthesia-producing drug. Accordingly, Gervitz discloses the administration ketamine to produce amnesia and fentanyl to produce sedation. Gervitz does not, however, disclose a tolerance-attenuating dose of ketamine when administered in combination with morphine. In fact, Gervitz neither teaches nor suggests tolerance attenuation or the need therefor. Accordingly, one of ordinary skill in the art would not appreciate, based on a reading of Gervitz, that morphine could be administered concurrently with a tolerance-attenuating dose of a ketamine to attenuate, reverse, or prevent tolerance to analgesics.

With regard to Lin, the Examiner alleges that Lin teaches that it is well known in the art that an NMDA receptor antagonist can abolish nociceptor hypersensitivity. Although Lin suggests a possible synergy between morphine, bupivacaine and ketamine, Lin does not disclose a tolerance-attenuating dose of ketamine when administered in combination with morphine. In fact, Lin neither teaches nor suggests tolerance attenuation or the need therefor. Accordingly, one of ordinary skill in the art would not appreciate, based on a reading of Lin, that morphine could be administered concurrently with a tolerance-attenuating dose of a ketamine to attenuate, reverse, or prevent tolerance to analgesics.

None of Elkhoury, Yaksh, Mayer, Gervitz and Lin alone, or in combination, teaches or suggests topical pharmaceutical compositions and methods of providing analgesia comprising morphine and a tolerance-attenuating dosage of ketamine sufficient to yield a dose-lowering effect on morphine. Similarly, one of ordinary skill in the art would not be motivated to modify the teachings of Elkhoury in light of Yaksh, Mayer, Gervitz and Lin to arrive at the claimed invention. Accordingly, reconsideration and withdrawal of the rejection to claims 1, 9, 14, 15, 19-22, and 27 under 35 U.S.C. § 103 are respectfully requested.

B. Claims 7, 8, 28, and 29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Elkhoury, Yaksh, Mayer, Gervitz and Lin, in further view of United States Patent No. 5,322,683 to Mackles et al. ("Mackles").

As discussed above, none of Elkhoury, Yaksh, Mayer, Gervitz and Lin alone, or in combination, teach or suggest topical pharmaceutical compositions and methods of providing

analgesia comprising morphine and a tolerance-attenuating dosage of ketamine sufficient to yield a dose-lowering effect on morphine.

In regard to Mackles, the Examiner alleges that Mackles teaches that lidocaine is a topical analgesic. Mackles does not teach or suggest the use of lidocaine in combination with any other active ingredients, let alone morphine and a tolerance-attenuating dosage of ketamine sufficient to yield a dose-lowering effect on morphine. One of ordinary skill in the art would not be motivated, based on a reading of Mackles, that lidocaine could be administered with morphine and a tolerance-attenuating dose of a ketamine to attenuate, reverse, or prevent tolerance to analgesics. Accordingly, reconsideration and withdrawal of the rejection to claims 7, 8, 28, and 29 under 35 U.S.C. § 103 is respectfully requested.

In short, the Examiner's rejection of the pending claims under 35 U.S.C. §103 is nothing more than an impermissible hindsight reconstruction of the claimed invention relying solely on Applicants' own teachings. *See, e.g., Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988).

In each of the obviousness rejections set forth above, the Examiner relies on a combination of no less than five references to pick and choose the individual elements of the claims without providing any motivation as to why one or ordinary skill in the art would be motivated to consult a particular reference and then combine it with the other references. In particular, the Examiner has chosen discrete disclosures from each of the supplementary references to arrive at his conclusion without demonstrating where in each reference the motivation to combine the reference with the primary reference, let alone with the other supplementary references, is taught. In some instances, the Examiner has relied upon a single sentence taken out of context. It has long been established that a single line in a prior art reference should not be taken out of context and relied upon with the benefit of hindsight to show obviousness. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, (Fed. Cir.1986).

By relying on numerous references, the Examiner appears to have 'skirted all around' the claimed invention without showing where or how the references suggest the claimed invention. This is improper. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 USPQ 81, 93 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 USPQ 543 (Fed. Cir. 1985).

III. Double Patenting Rejections

Claims 1, 7-9, 14, 15, 19-22 and 27-29 stand rejected on the grounds of nonstatutory obviousness-type double patenting over claims 2 and 11-15 of United States Patent No. 6,825,203. Claims 1, 9, 14, 15, 19-22 and 27 further stand rejected on the grounds of nonstatutory obviousness-type double patenting over claims 27-35 of copending U.S. Application Serial No. 10/823,365.

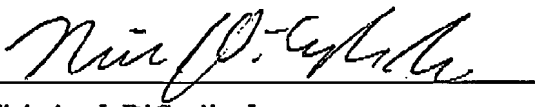
It still remains unknown what subject matter claimed and disclosed in the present application will be deemed allowable. Hence any statement regarding these rejections made on Applicants' part would be premature. Therefore, Applicants respectfully traverse these rejections, and maintain the request that these rejections be held in abeyance until subject matter is deemed allowable in this application.

CONCLUSION

Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date and the Examiner is invited to contact the undersigned at the telephone number indicated below to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 04-1105.

Date: May 14, 2007

Respectfully submitted,



Nicholas J. DiCeglie, Jr.
Registration No.: 51,615
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, MA 02205
Attorneys for Applicants
Telephone: 203-975-7505